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Cost-Effectiveness of Neoadjuvant Chemotherapy versus Primary Surgery in Elderly Patients with Advanced Ovarian Cancer

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ABSTRACT

Background: The use of neoadjuvant chemotherapy (NAC) in the treatment of advanced ovarian cancer has increased in recent years. There is uncertainty about NAC's effectiveness and no study of its cost-effectiveness compared with that of standard primary debulking surgery (PDS). **Objectives:** To seek answers to three important questions: 1) What is the lifetime cost of treating elderly patients with advanced ovarian cancer, based on the primary treatment received? 2) Are the extra costs expended by the NAC group worth any extra survival advantage? 3) Would NAC potentially benefit a particular subgroup and serve as a cost-effective first-line treatment approach? **Methods:** A cohort of elderly women (≥65 years) with stage III/IV ovarian cancer was identified from the Surveillance, Epidemiology and End Results-Medicare linked database from January 1, 2000, to December 31, 2009. Cost analysis was conducted from a payer perspective, and direct medical costs incurred by Medicare were integrated for each patient. Cumulative treatment costs were estimated with a phase-of-care approach, and effectiveness was measured as years of survival. Incremental cost-effectiveness ratio (ICER) and propensity-score–adjusted net monetary benefit regression was used to estimate the cost-effectiveness of NAC per life-year gained. Analyses were further stratified by risk group categorization on the basis of tumor stage, patient age, and comorbidity score. **Results:** Average lifetime cost for treatment with NAC was $17,417 more than with PDS. With only 0.1 incremental life-year gained, the ICER estimate was $174,173. Stratification, however, helped to delineate the treatment effect. Patients in the high-risk subgroup incurred $34,390 and 0.8 life-years more than did patients in the PDS subgroup, with a corresponding ICER of $42,987. In the non–high-risk subgroup, NAC use was dominated by PDS (more costly, less effective). **Conclusions:** Administering NAC before surgery to patients in the high-risk subgroup was cost-effective at "normal" levels of willingness to pay, but not for the overall sample or for patients in the non–high-risk subgroup.

Keywords: cost-effectiveness, neoadjuvant chemotherapy, primary debulking surgery, ovarian cancer.

Introduction

Ovarian cancer accounts for only 3% of all cancers in women in the United States [1], yet it is the leading cause of death from gynecologic malignancies, with elderly women experiencing a significantly greater burden of this disease [2]. Despite a 5-year survival rate of 95% in women with stage I disease, 60% to 75% of the cases are diagnosed at an advanced stage, wherein survival is dramatically reduced to about 30%; a poor prognosis [2,3]. Primary debulking surgery (PDS) followed by adjuvant chemotherapy (AC) has remained the standard approach to treat advanced stage III/IV ovarian cancer for decades. Surgical debulking is the standard treatment for this malignancy, with its success lying in optimally reducing the macroscopic tumor lump to less than 1 cm in size. More recently, experts report that optimal resection entails no macroscopic tumor residue after surgery [4]. Clinical characteristics (e.g., bulky unresectable tumor or poor performance status), however, often present a challenge in performing optimal first-line surgical resection and patients may instead be given neoadjuvant chemotherapy (NAC) before debulking surgery; that is, a few cycles of chemotherapy are followed by delayed debulking surgery [5]. This method helps to overcome the surgical difficulties of treating complex disease and reduces the tumor to a manageable size for optimum cytoreduction.

The effectiveness of NAC versus PDS has been studied over the last two decades. Studies have highlighted the mixed effects

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of NAC on survival and perioperative morbidity, but were limited to nonrandomized small sample or retrospective evaluations (see Onda and Yoshikawa [6] for a review). A meta-analysis of 22 cohorts reported that platinum-based NAC was associated with inferior overall survival compared with PDS-AC [7]. In contrast, a subsequent meta-analysis concluded that NAC reduced the risk of suboptimal surgery by half and may also help gynecologic oncologists enhance the rate of optimal cytoreduction [8]. Findings from meta-analyses are dependent on the kind of studies included, as well as different statistical analysis performed. The age of patients included in these studies ranged from 53 to 68 years and may not be generalizable to elderly women (i.e., 65+ years). Of four prospective randomized phase III trials initiated to date [9–12], results from the European Organisation for Research and Treatment of Cancer (EORTC) and Medical Research Council-Chemotherapy or Upfront Surgery in Ovarian Cancer Patients trials have reported noninferior survival with significantly less morbidity in patients with stage IIIc/IV cancer receiving NAC [9,11]. Although other phase III trials are underway, exploratory subgroup findings from the EORTC trial reveal that patients with stage IV cancer and bulky metastatic tumors may have a longer survival from NAC [13]. Although members of the Society of Gynecologic Oncologists in the United States are not fully convinced of NAC as a treatment option [14], population-based evidence has shown that from 1995 to 2005 there has been a small decline in the use of PDS, with a corresponding increase in the odds of use of NAC in elderly patients with ovarian cancer [15]. Almost 14% of advanced cases (n = 6844) received NAC and experienced fewer postsurgical complications than did those receiving PDS [16]. Thus, we anticipate a slow growing use of NAC in routine clinical practice. An aging population and possible change in treatment paradigm over the years can be expected to contribute to the strain on Medicare resources. Because administering chemotherapy before debulking will likely increase health care utilization, concerns about cost-effectiveness will likely arise, despite favorable outcomes for some patients.

Economic evaluations within the realm of ovarian cancer have largely centered on cost-effectiveness studies evaluating various chemotherapeutic agents for de novo [17–24] and recurrent [25–30] cases of cancer or assessing the value of intraperitoneal chemotherapy compared with intravenous administration [31,32]. Most of the cost-effectiveness estimates were based on modeling approaches using several data sources and results from clinical trials. Economic assessment involving the use of NAC in ovarian cancer has not been explored, despite its anticipated increasing use in community practice. We sought answers to three important questions: 1) What is the lifetime cost of treating elderly patients with advanced ovarian cancer, based on the primary treatment received? 2) Are the extra costs expended by the NAC group worth any extra survival advantage? 3) Would NAC potentially benefit a particular subgroup and serve as a cost-effective first-line treatment approach?

Methods

Data Source, Cohort Selection, and Treatment Identification

This was a retrospective cohort study that used data from the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database [33,34]. We included women 65 years or older and newly diagnosed with advanced stage III/IV epithelial ovarian cancer from January 1, 2000, to December 31, 2009, with their Medicare claims through 2010 (n = 8188). For information on SEER-Medicare data and details on the cohort selection, see Appendix A in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.01.005. Treatment received was identified on the basis of first claim after ovarian cancer diagnosis from Medicare claims data. Cases with no evidence of surgery or chemotherapy within 12 months of diagnosis were excluded (n = 1810). Patients receiving surgery as first-line treatment within 12 months from diagnosis (may or may not be given AC) were classified as having received PDS and were identified from Medicare claims or from cancer-directed surgery codes in SEER data. Although our PDS definition may be less stringent than that used in trials [10], a frequency distribution for cancer-directed surgery codes showed that most of the patients belonged to code 60 (debulking; cytoreductive surgery, not otherwise specified; n = 1340) or code 61 (with colon [including appendix] and/or small intestine resection [not incidental]; n = 1208). None of the patients in our study had SEER-surgery codes 10-16, 20-22, or 30-32, which may be more characteristic of surgery for early stage ovarian cancer. Hence, our definition for PDS would match closely with that used in clinical trials. Patients receiving chemotherapy as first-line treatment within 12 months of diagnosis and before the date of surgery were classified as having received NAC (see Appendix A, Tables 2–4, in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.01.005 for codes used to define PDS and NAC). Patients who did not receive surgery after primary chemotherapy were excluded (n = 1535).

Data Analysis

Patient characteristics were described by primary treatment, with statistically significant differences identified using *t* tests for continuous variables and chi-square tests for categorical variables. Treatment assignment is not randomized in routine clinical care, and there may be baseline differences in patient and clinical characteristics. Traditionally used multivariate-regression methods that adjust for confounding bias pose a threat in situations in which there is lack of overlap between treatment groups. Patients with complete contraindications and those with absolute indications for the treatment are not easily identified with the conventional method, leading to model-misspecification and biased estimates of treatment effects [35,36]. Hence, we used the propensity score (PS) method to adjust for baseline characteristic differences between treatment groups when evaluating cost, effectiveness, and cost-effectiveness measures. PS is the conditional probability of being treated given the observed baseline covariates [37]. Using the logistic regression model, a PS was estimated to predict the probability of treatment assignment (dependent variable) for each patient from covariates listed in Table 1. Quintiles of PS were computed to stratify patients into mutually exclusive groups, so that across strata, patients with either treatment alternative have a similar distribution of measured covariates. This method can eliminate almost 90% of the bias owing to unbalanced treatment groups [38], and hence can provide better control of bias over traditional multivariate regressions. Considerable overlap was seen in plots of PS distribution for both treatment groups, and the last column in Table 1 shows that after adjustment with PS quintiles, balance was achieved in the distribution of covariates between treatment groups. Computer programming and analysis were carried out using SAS version 9.3 (SAS Institute, Inc., Cary, NC).

Estimating Costs

Total treatment costs were estimated starting from the date of diagnosis until death or last available Medicare claims (December 2010), using the phase-of-care approach [39]. This method is popularly used to estimate costs in the presence of censored data [40,41], wherein the period between cancer diagnosis and death was divided into three phases of care—initial, continuing, and terminal—depending on patient survival time (see Appendix A, Table 7, in Supplemental Materials found at http://dx.doi.org/

Table 1 – Distribution of covariates in patients with advanced ovarian cancer by primary treatment.

Variable	Total	NAC	PDS	P value	
	(n = 4843)	(n = 591)	(n = 4252)	Before PS adjustment	After PS adjustment
Sociodemographic characteristics					
Age (y)					
Mean (range)	74.8 (65-100)	74.1 (65-97)	74.9 (65-100)		
65–69	1101 (22.8)	149 (25.2)	954 (22.4)	0.0203	0.7029
70–74	1383 (28.6)	191 (32.3)	1192 (28.0)		
75–79	1320 (27.3)	145 (24.5)	1175 (27.6)		
80–84	738 (15.2)	80 (13.5)	658 (15.5)		
85+	299 (6.2)	26 (4.4)	273 (6.4)		
Race					
White	4474 (92.4)	535 (90.5)	3939 (92.6)	0.0695	0.9228
Nonwhite	369 (7.6)	56 (9.5)	313 (7.4)		
Marital status					
Married	2301 (47.5)	296 (50.1)	2005 (47.1)	0.4017	0.9160
Nonmarried	2389 (49.3)	288 (48.7)	2101 (49.4)		
Median household income					
First quartile (high)	1157 (23.9)	169 (28.6)	988 (23.2)	0.0308	0.5325
Second quartile	1157 (23.9)	139 (23.5)	1018 (23.9)		
Third quartile	1156 (23.9)	129 (21.8)	1027 (24.1)		
Fourth quartile (low)	1167 (24.1)	129 (21.8)	1038 (24.4)		
Clinical characteristics					
Stage					
Stage III	2725 (56.3)	274 (46.4)	2451 (57.6)	<0.0001	0.5690
Stage IV	1576 (32.5)	255 (43.1)	1321 (31.1)		
Stage distant NOS	542 (11.2)	62 (10.5)	480 (11.3)		
Histology					
Serous	3252 (67.1)	371 (62.8)	2881 (67.8)	0.0157	0.5192
Other epithelial	1591 (32.8)	220 (37.2)	1371 (32.2)		
Grade					
Well/moderately differentiated	742 (15.3)	55 (9.3)	687 (16.2)	<0.0001	0.0878
Poorly/undifferentiated	3136 (64.7)	332 (56.2)	2804 (65.9)		
Not determined/stated/applicable	965 (19.9)	204 (34.5)	761 (17.9)		
Comorbidity					
0	2969 (61.3)	377 (63.8)	2592 (61.0)	0.1970	0.7819
1	1177 (24.3)	146 (24.7)	1031 (24.2)		
2	420 (8.7)	42 (7.1)	378 (8.9)		
3+	277 (5.7)	26 (4.4)	251 (5.9)		
Year of diagnosis					
2000–2001	956 (19.7)	94 (15.9)	862 (20.3)	0.0002	0.4657
2002–2003	988 (20.4)	95 (16.1)	893 (21.0)		
2004–2005	882 (18.2)	109 (18.4)	773 (18.2)		
2006–2007	1035 (21.4)	145 (24.5)	890 (20.9)		
2008–2009	982 (20.3)	148 (25.0)	834 (19.6)		
Access					
SEER area					
Northeast	1099 (22.7)	135 (22.8)	964 (22.7)	0.0003	0.7837
South	926 (19.1)	101 (17.1)	825 (19.4)		
Midwest	633 (13.1)	50 (8.5)	583 (13.7)		
West	2185 (45.1)	305 (51.6)	1880 (44.2)		
Locality type					
Big metro/metro/urban	4369 (90.2)	545 (92.2)	3824 (89.9)	0.0802	0.6947
Less urban/rural	474 (9.8)	46 (7.8)	428 (10.1)		
Treatment facility					
NCI comprehensive cancer center	368 (7.6)	90 (15.3)	278 (6.5)	<0.0001	0.0656
Other facility with <300 beds	1394 (28.8)	145 (24.5)	1249 (29.4)		
Other facility with ≥300 beds	2997 (61.9)	351 (59.4)	2646 (62.2)		

Note. Values are n (%).

NAC, neoadjuvant chemotherapy; NCI, National Cancer Institute; NOS, not otherwise specified; PDS, primary debulking surgery; PS, propensity score; SEER, Surveillance, Epidemiology and End Results.

10.1016/j.jval.2015.01.005 for definition of phases and distribution of costs by phases). We incorporated total health care costs compared with only cancer-related expenditures because it gives a complete indicator of health care burden in elderly patients with cancer. Direct medical costs, using Medicare payments (rather than billed charges), were identified from claims data and adjusted to 2009 constant dollars using Centers for Medicare & Medicaid Services adjusters for geographic variation and inflation over time, for both Part A and Part B claims (for details on Centers for Medicare & Medicaid Services adjusters, see Brown et al. [40]). Cumulative reimbursement amounts were added from various Medicare files and allocated to appropriate phases to determine phase-specific costs for each patient. Lifetime costs were estimated for both treatment groups by combining the mean phase-specific costs weighted with the survival function [42]. Costs were also segregated by major cost categories (e.g., surgery-related hospital, physician, and complications costs and chemotherapy and related adverse effects costs) to examine any potential cost category influencing treatment group differences (see Appendix A, Tables 5 and 6, in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.01.005 for codes).

Estimating Effectiveness

Effectiveness was measured as the observed improvement in overall survival between treatment alternatives, wherein patients were followed from diagnosis until death or end of the follow-up period (December 31, 2011). Patients not experiencing the event (death) by this date were censored. Parametric regression models (using LIFEREG in SAS) were also run to estimate treatment effect on survival. The results obtained using parametric models were comparable to that obtained using the Kaplan-Meir method and hence not reported. In addition, the effect of treatment on survival was compared within each stratum of the PS quintile and the average treatment effects were estimated using the Cox proportional hazards regression, adjusting for PS.

Estimating Cost-Effectiveness

From a payer perspective (i.e., Medicare), we estimated incremental cost-effectiveness ratios (ICERs) and net monetary benefits (NMBs) to assess the cost-effectiveness of NAC [43–46], measured per life-year gained.

1. ICER: Using average and median values of costs and effectiveness, we estimated mean and median ICER as the ratio of the difference in average (or median) costs to the difference in average (or median) life-years between two treatment alternatives. Confidence intervals (CIs) for ICERs were estimated using nonparametric bootstrapping, with 2.5th and 97.5th percentiles of the bootstrap samples used as an approximation of the 95% CI.
2. NMB: For each patient with ovarian cancer, a net benefit (NB) value was calculated before regression, for varying willingness-to-pay (WTP) values (λ). Several NB regression models were then run to obtain crude and PS-adjusted estimates for incremental NB ($NB_{NAC} - NB_{PDS}$), each with a different value for λ.

$$NB = (\text{Willingness to pay} \times \text{Effect}) - \text{cost} = \lambda b_i - c_i$$

$$\text{Crude model: } NB = \beta_0 + \beta_{TX}(TX_i) + \varepsilon_i$$

$$\text{PS-adjusted model: } NB = \beta_0 + \beta_{TX}(TX_i) + \Sigma\beta_j X(j) + \varepsilon_i$$

In the above equations, TX_i indicates treatment group (TX = 0 for PDS and TX = 1 for NAC), b_i represents years of survival, c_i indicates total costs for patient i, $X(j)$ indicates a vector of covariates that include PS, and β_{TX} represents the incremental NB. Cost and effectiveness measures were discounted at an annual 3% rate. Cost-effectiveness acceptability curves were graphed to assess uncertainty in NMB estimates. A curve of the probability that NAC is cost-effective was plotted against a series of WTP thresholds.

Subgroup Analysis

Although prognosis of ovarian cancer is highly dependent on residual tumor mass after surgery, postoperative outcomes vary on the basis of stage, age, and comorbidity score of the patient [47,48]. Hence, to explore the potential heterogeneity of effects, women were also grouped into a high-risk category (age 75+ years and stage IV or age 75+ years, stage III/advanced stage and comorbidity score $\geq$1) or a non–high-risk category that we adapted from previously published criteria [16,48], and the value of NAC was determined for these subgroups separately.

Results

Of 4843 women who met the study eligibility criteria, 12% (n = 591) received NAC before surgery and 88% (n = 4252) received PDS with/without AC. Although half the study population comprised nonmarried women (49%) aged 75 years and older (49%), the majority of the study population was white (92%). Most patients were diagnosed with stage III (56%), serous epithelial histology (67%) tumor. Table 1 presents patient characteristics for the overall sample and by treatment received. Although significant differences between the treatment groups were observed for most baseline covariates, they were similar based on race, marital status, comorbidity score, and locality type. Compared with patients receiving NAC, patients receiving PDS more commonly presented with stage III (58% vs. 46%) and well to moderately differentiated grade tumor (16% vs. 9%).

Table 2 presents average and median health care costs by phase of care and treatment group. Observed costs (undiscounted and 3% discounted) in the continuing phase were higher than in initial and terminal phases. Cumulative lifetime costs were higher for the NAC group (mean $134,576; median $123,595) than for the PDS group (mean $117,159; median $100,747). After accounting for censoring, there was an increase in continuing phase costs, resulting in an increase in mean and median lifetime costs by $38,851 and $21,074 for the NAC group and $51,137 and $20,256 for the PDS group, respectively. On comparing cost categories, it was found that patients receiving NAC incurred significantly lower surgical complication costs (–$4987; $P = 0.0007$), but higher chemotherapy ($6874; $P < 0.0001$) and chemotherapy-related adverse effects costs ($4604; $P = 0.0001$) in the 12 months after diagnosis, after adjusting for PS. No significant differences were observed for surgery-related hospital ($P = 0.2826$) and physician ($P = 0.1572$) cost categories (see Appendix B, Table 1, in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.01.005).

Crude and adjusted overall survival was compared across treatment groups in Figures 1 and 2 and Table 2 in Appendix B in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.01.005. NAC did not improve survival, for the entire sample and also within strata of PS quintiles (PS-adjusted hazard ratio = 0.947; 95% CI 0.855–1.049). A very small difference was observed in mean and median overall survival between patients who received NAC (mean life-years = 3.1, median life-years = 2.4) and patients who received PDS (mean life-years = 3.0, median life-years = 2.1). The results for the cost-effectiveness of NAC using the ICER and NMB approach are presented in Table 3. For each life-year gained, the mean and median ICER for the NAC group compared with the PDS group was $174,173 and $76,160,

Table 2 – Total health care cost* based on phase-of-care approach.

Treatment	n	Observed mean costs ($)		Estimated mean costs ($)	Observed median costs ($)		Estimated median costs ($)
		Undiscounted	3% discount rate	Discounted & weighted with survival	Undiscounted	3% discount rate	Discounted & weighted with survival
Initial-phase cost							
NAC	569	47,502.7	47,179.1	48,348.6	45,534.4	45,296.1	44,419.6
PDS	3,388	49,126.2	48,912.9	45,420.2	45,685.4	45,426.6	38,261.5
Continuing-phase cost							
NAC	510	67,123.3	63,469.7	88,007.0	50,606.4	48,786.4	69,048.1
PDS	2,983	68,784.5	64,111.2	69,741.2	47,591.5	45,156.4	49,865.5
Terminal-phase cost							
NAC	471	45,422.9	43,142.6	37,072.2	40,285.8	37,099.3	31,201.4
PDS	3,463	42,728.9	40,773.8	53,134.2	35,161.0	33,320.7	32,875.9
Lifetime total costs							
NAC	591	139,858.1	134,576.3	173,427.7	127,871.7	123,595.4	144,669.1
PDS	4,252	122,199.9	117,159.0	168,295.6	103,754.0	100,747.3	121,002.9

Note. Appendix A outlines the steps used to obtain the values in this table.
NAC, neoadjuvant chemotherapy; PDS, primary debulking surgery.
* Adjusted for geographic variation and inflation over time.

respectively, with wide 95% CI indicating uncertainty around the point estimates. The NMB regression analyses show that administering NAC is not cost-effective at lower WTP thresholds. Negative NMBs were obtained if the payer's WTP was $100,000 or lower per life-year. Although there may be a positive NMB if the WTP per life-year is at least $200,000 or higher, the estimates lack precision given the wide CI. The corresponding cost-effectiveness acceptability curve displayed in Figure 1 depicts this uncertainty. For example, at a WTP of $100,000 there is a 42% chance that the intervention is cost-effective, whereas at a WTP of $200,000 the probability of NAC being cost-effective increases to 72%.

Subgroup analysis results are presented in Table 4. About 30% of the total sample (n = 1452) comprised a high-risk group and the remaining 3391 women belonged to the non–high-risk group. Figure 3 in Appendix B in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.01.005 shows significant survival benefits using NAC in the high-risk subgroup (mean incremental effectiveness = 0.8 years), with a corresponding incremental mean health care cost of $34,390. The mean and median ICER for NAC in the high-risk subgroup was estimated as $42,987 (95% CI $28,150–$66,169) and $27,332 (95% CI $22,912–$49,964), respectively. In contrast, the mean and median ICER for the non–high-risk subgroup indicate that the use of NAC was dominated by PDS, owing to the observed negative survival benefit and higher cost spending. Similarly, using NMB regression we found that treating patients in the high-risk subgroup with NAC before surgery had positive NMBs for all WTP values of $50,000 and above, while patients in the non–high-risk subgroup had negative NMBs for any value that the payer was willing to spend. As seen in Figure 2, the probability that NAC is cost-effective is less than 11% across the spectrum of WTP values for non–high-risk patients, but holds major value when administered to high-risk patients (i.e., ~80% or higher chance of being cost-effective for all WTP thresholds ≥$50,000).

Discussion

Treating elderly patients with ovarian cancer is not straightforward as evident from clinical trial data, especially as diagnosis occurs at advanced stages and the 5-year survival rate is relatively lower than for other malignancies. Controversy surrounding the benefit of NAC has so far been limited to morbidity and survival measures. Cost issues, however, will likely emerge as the use of NAC will increase in clinical practice. While experts continue to weigh the effectiveness of NAC in real world, we undertook a cost-effectiveness analysis to inform clinical and policy decision makers about the economic implications of NAC in perspective. We identified a high-risk subgroup that may potentially gain health benefits from NAC use and will be an economically attractive resource allocation from a payer perspective.

The average total cost for patients receiving NAC was 15% higher than for patients receiving PDS (i.e., $134,576 vs. $117,159). Although survival analysis techniques have been used to obtain reweighted estimators for mean health care costs, it may result in biased estimates in the presence of censored data, and hence investigators have discouraged its use [42,49]. Independence between time-to-event and time-to-censoring is a key requirement for Kaplan-Meier survival curve. The same principle, however, may not be applicable in the cost scenario because cumulative cost-to-event and cumulative cost-to-censoring are dependent on a patient's unique pattern of cost accumulation. Thus, we used the recommended phase-based costing method to estimate lifetime costs of the entire cohort without actually observing costs for all patients across their lifetime. After weighting with survival, mean costs in both groups increased (NAC = $173,428; PDS = $168,296), indicating that observed costs are underestimated when observations are censored. Notably, there was an increase in the continuing-phase costs, which may be explained by the disease's high recurrence rate. Almost 70% to 90% of advanced cases are reported to experience a recurrence [50] wherein cancer treatment may continue invariably longer through the continuous phase. Extensive surveillance and many cycles of chemotherapy (maintenance or recurrence) could potentially drive high costs in this phase. Cost studies in Europe and Australia have estimated chemotherapeutic costs as the prime component of total costs when treating ovarian cancer [51,52]. Thus, when dealing with censored observations, studying lifetime costs becomes important to estimate overall

Table 3 – Cost-effectiveness of using neoadjuvant chemotherapy in patients with advanced ovarian cancer.

	Undiscounted		Discounted at 3%	
Total health care costs ($)	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**
NAC	139,858.1 ± 78,964.7	127,871.7	134,576.3 ± 73,512.0	123,595.4
PDS	122,199.9 ± 91,545.4	103,754.0	117,159.0 ± 85,471.1	100,747.3
Δ Cost	17,658.2	24,117.7	17,417.3	22,848.1
Effectiveness (life-years)	**Mean (SE)**	**Median**	**Mean (SE)**	**Median**
NAC	3.3 (0.1)	2.4	3.1 (0.1)	2.4
PDS	3.2 (0.1)	2.1	3.0 (0.0)	2.1
Δ Effectiveness	0.1	0.3	0.1	0.3
ICER ($)	**Mean ICER per LYG (95% CI)**	**Median ICER per LYG (95% CI)**	**Mean ICER per LYG (95% CI)**	**Median ICER per LYG (95% CI)**
NAC	176,582 (−2,166,732 to 3,167,860)	80,392.3 (60,582–252,151)	174,173 (−1,840,486 to 1,938,920)	76,160.3 (60,003–250,992)
	Undiscounted		Discounted at 3%	
NMB analysis on NAC	**Crude NMB (*P* value)**	**PS-adjusted NMB (*P* value)**	**Crude NMB (*P* value)**	**PS-adjusted NMB (*P* value)**
WTP value ($ per LYG)				
25,000	−16,139 (<0.0001)	−12,298 (0.0017)	−15,265 (<0.0001)	−11,516 (0.0017)
50,000	−14,620 (0.0038)	−9,484.8 (0.0745)	−13,114 (0.0049)	−8,313.4 (0.0896)
100,000	−11,583 (0.2202)	−3,859.2 (0.6986)	−8,809.8 (0.3034)	−1,907.4 (0.8327)
200,000	−5,506.9 (0.7770)	7,392.0 (0.7189)	−202.3 (0.9908)	10,905 (0.5558)
400,000	6,644.4 (0.8681)	29,894 (0.4795)	17,013 (0.6367)	36,529 (0.3371)
800,000	30,947 (0.7039)	74,899 (0.3840)	51,442 (0.4826)	87,777 (0.2568)
1,000,000	43,098 (0.6731)	97,402 (0.3669)	68,657 (0.4551)	113,401 (0.2429)

CI, confidence interval; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NAC, neoadjuvant chemotherapy; NMB, net monetary benefit; PDS, primary debulking surgery; PS, propensity score; SE, standard error; WTP, willingness to pay.

disease burden. Segregating costs by important categories revealed differences across treatment groups that were in the expected direction. Surgical complication–related costs were higher for the PDS group, which appears to be directly proportional to findings from earlier studies that report higher blood loss, blood transfusions, peri- and postoperative morbidity, longer intensive care unit stays, and overall greater use of hospital resources in those receiving PDS [53–57]. Similarly, an earlier study using the SEER-Medicare data set found that patients receiving NAC received almost twice the median number of chemotherapy cycles than did those receiving PDS [16], which potentially explains the higher incurred chemotherapy and chemotherapy-related adverse effects costs that we observed in this group.

To our knowledge, this is the first study to evaluate the cost-effectiveness of administering chemotherapy before PDS in patients with advanced ovarian cancer. With a modest increase in cost and no meaningful survival benefit, NAC is not cost-effective for all patients. The NMB regression depicts that uncertainty related to NAC use fluctuates considerably as WTP varies. For example, when WTP is within $50,000 of the ICER, the probability of NAC being cost-effective ranges from 42% to 72%.

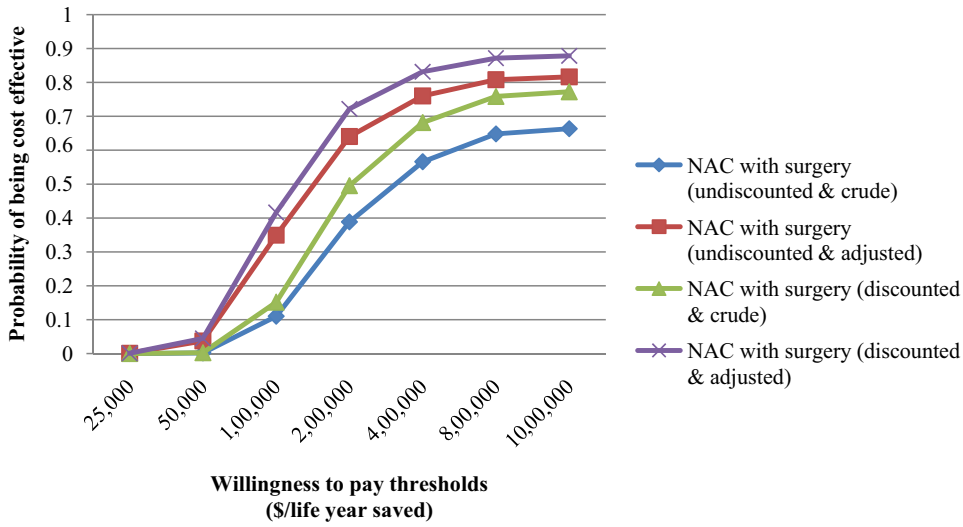

Fig. 1 – Cost-effectiveness acceptability curve for overall sample. NAC, neoadjuvant chemotherapy.

Table 4 – Cost-effectiveness* of using neoadjuvant chemotherapy in patients with advanced ovarian cancer, stratified by risk group.†

	High risk (n = 1452)		Non–high risk (n = 3391)	
Total health care costs ($)	**Mean ± SD**	**Median**	**Mean ± SD**	**Median**
NAC	131,657.6 ± 69,627.1	116,213.1	135,678.5 ± 74,975.8	126,230.0
PDS	97,267.8 ± 74,683.1	80,681.8	125,822.0 ± 88,388.0	108,493.8
Δ Cost	34,389.8	35,531.3	9,856.5	17,736.2
Effectiveness (life-years)	**Mean (SE)**	**Median**	**Mean (SE)**	**Median**
NAC	2.9 (0.2)	2.6	3.0 (0.1)	2.3
PDS	2.1 (0.1)	1.3	3.3 (0.1)	2.4
Δ Effectiveness	0.8	1.3	−0.3	−0.1
ICER ($)	**Mean ICER per LYG (95% CI)**	**Median ICER per LYG (95% CI)**	**Mean ICER per LYG (95% CI)**	**Median ICER per LYG (95% CI)**
NAC	42,987.2 (28,150–66,169)	27,331.8 (22,912–49,964)	Dominated	Dominated
NMB analysis on NAC	**Crude NMB (*P* value)**	**PS-adjusted NMB (*P* value)**	**Crude NMB (*P* value)**	**PS-adjusted NMB (*P* value)**
WTP value ($ per LYG)				
25,000	−14,156 (0.0104)	−14,398 (0.0151)	−15,486 (0.0004)	−11,001 (0.0156)
50,000	6,078.6 (0.4060)	4,991.6 (0.5312)	−21,116 (0.0003)	−14,331 (0.0180)
100,000	46,547 (0.0008)	43,770 (0.0041)	−32,376 (0.0021)	−20,990 (0.0552)
200,000	127,484 (<0.0001)	121,328 (0.0001)	−54,895 (0.0098)	−34,310 (0.1216)
400,000	289,357 (<0.0001)	276,443 (<0.0001)	−99,933 (0.0215)	−60,949 (0.1787)
800,000	613,104 (<0.0001)	586,672 (<0.0001)	−190,010 (0.0312)	−114,226 (0.2143)
1,000,000	774,978 (<0.0001)	741,787 (<0.0001)	−235,048 (0.0335)	−140,865 (0.2219)

CI, confidence interval; ICER, incremental cost-effectiveness ratio; LYG, life-years gained; NAC, neoadjuvant chemotherapy; NMB, net monetary benefit; PDS, primary debulking surgery; PS, propensity score; SE, standard error; WTP, willingness to pay.

* Using a 3% discount rate for costs and effectiveness.

† Classified on the basis of age, stage, and Charlson comorbidity index [33].

On stratifying results by risk groups, significant survival advantage was observed in the high-risk subgroup. This is consistent with the EORTC trial and other retrospective studies that reported an improved survival with the use of NAC in patients characterized by stage IV tumor, older age, and poor performance status [13,16]. The ICER for NAC in high-risk subgroup was $42,988 per life-year saved, with corresponding NMB analysis supporting its use as a cost-effective intervention at "normal" levels of WTP. For a traditional $100,000 that the payer may be willing to pay, the uncertainty associated with NAC was less than 5% for each extra survival year in high-risk patients, as compared with PDS. For the non–high-risk subgroup, however, greater health care spending in the NAC group did not translate into any improved survival (NAC was dominated by PDS). Combining the subgroups masks this important finding. These results from the stratified analysis concur with expert reports [4,58] and guidelines [59] that encourage the use of PDS as the standard first-line treatment in patients with stage II or higher cancer, while recommending the use of NAC only for certain patient subgroups contingent on clinical expertise. For policy purposes, ICERs have traditionally been

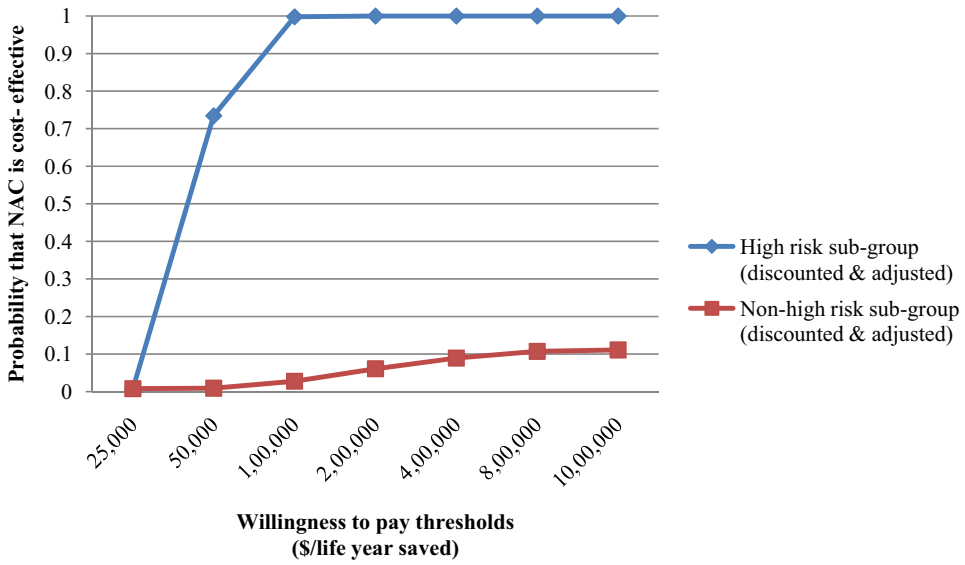

Fig. 2 – Cost-effectiveness acceptability curve stratified by risk subgroup. NAC, neoadjuvant chemotherapy.

estimated using mean values of cost and effectiveness for alternative treatment groups. Recently, Bang and Zhao [60] discussed the merit in also reporting the median ICER [60]. Especially in situations in which effectiveness is measured in life-years and median survival time is an important outcome indicator, median-based ICER provides a holistic understanding of study findings. We observed considerable concordance in the direction of the mean and median ICER for our subgroup analysis though our full sample findings depicted considerable inconsistencies. Although the literature lacks any comparable study, we identified a few studies that have estimated other aspects of clinical management. For example, using community-level data from the Mayo clinic, Aletti et al. [61] showed that an aggressive and complex surgical approach has a cost-effectiveness ratio of $8912 per life-year gained compared with simple surgery in advanced ovarian cancer [61]. Similarly, Bristow et al. [62] and Greving et al. [63] have valued the place of varying treatment referral centers (e.g., expert center or tertiary referral care) in advanced-stage disease, while Lowery et al. [64] demonstrate the potential of early palliative care intervention for recurrent disease cases.

There are important limitations to consider in this study. Findings are restricted in generalizability based on the inclusion criteria that were applied. Despite the use of the population-based SEER-Medicare database, which provided a rich source of cost as well as long-term follow-up and outcomes data, limitations inherent to the nature of observational claims database are applicable (e.g., incomplete reporting, missing claims, and inaccurate out-of-pocket costs). Although we used PS methods to minimize potential selection bias arising from nonrandom treatment assignment, residual confounding due to unmeasured factors such as tumor distribution and extent of tumor resection may exist. Given their importance in prognosis, we recommend future studies to incorporate additional instrumental variable methods to account for some unmeasured confounders and add robustness to our statistical method. Finding an appropriate instrumental variable may be challenging; however, geographic variation has been increasingly used in comparative-effectiveness treatment studies using this data [65–67]. To guide policy decision making, cost data reflect only those that were paid by Medicare. Total treatment costs did not account for out-of-pocket payments (e.g., co-payments or deductibles) or nonmedical costs (e.g., patient time costs and travel costs) incurred by patients, lacking an overall societal evaluation. Over three-quarters of the study population, however, was older than 70 years, and costs related to departure from the workforce may be trivial as well as insignificant from a third-party payer perspective. Unlike previous studies that have reported costs for only a fixed duration [51,52], we accounted for censoring to give an estimate of lifetime costs related to treating advanced ovarian cancer and also adjusted costs for patient and clinical characteristics. Studying lifetime treatment cost is particularly relevant in this cohort because of the high tumor recurrence rate, which may necessitate continual chemotherapeutic treatment in the continuous phase of care and contribute substantially to the overall cost of treatment. Likewise, adverse effect costs (tangible and intangible) associated with extended cancer treatment cannot be ignored. Although quality of life did not significantly differ between treatment groups for patients enrolled in the EORTC trial [68], it would be important to assess whether the same holds true for this population. Because NAC provides better morbidity outcomes, including quality of life may tend to reinforce the basic findings.

In conclusion, chemotherapy use before surgery has a favorable cost-effectiveness profile in the high-risk group alone at classic WTP thresholds. Its use as a general first-line treatment in all patients is not supported, so strengthening the role of PDS as standard approach to treat advanced ovarian cancer. We suggest that future studies should evaluate the role of varying chemotherapeutic schedules in the NAC setting.

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Supplemental Materials

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